

**Biotechnology Medicinal Products:  
Opportunities, Challenges  
&  
the Implications for Follow-on Biologics**

# What we will talk about today

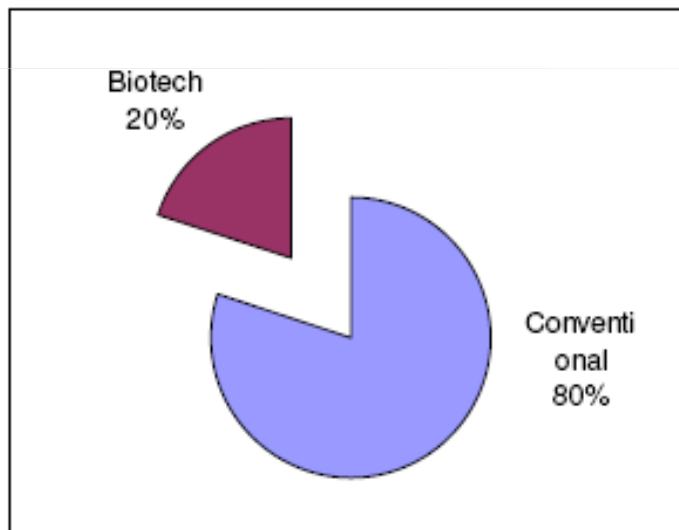
- About biotechnology medicines
  - Powerful medicines
  - Science of biologics
- Implications for follow-on biologics
  - Science, patient safety & innovation

# Growing importance of biotech medicines

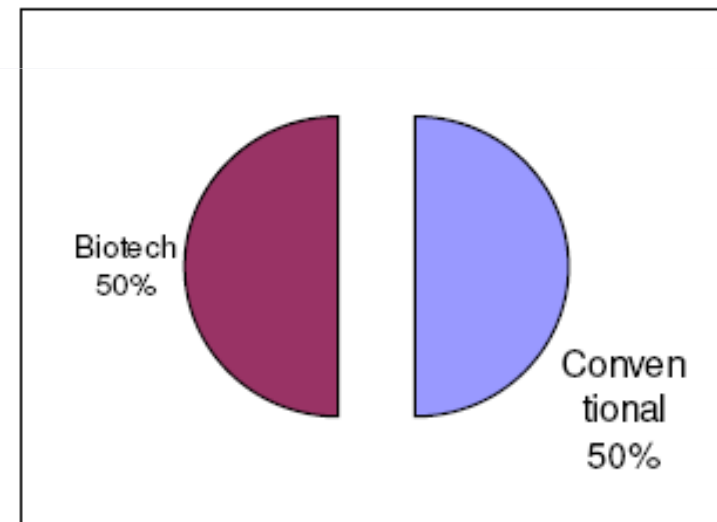
- Biotechnology medicines have been proven to be safe and effective with an excellent record of patient satisfaction and safety
- Biotechnology has produced medicines for some of the most serious and intractable diseases

# Development of Biotech Medicines Continues to Grow

Medicines on the market



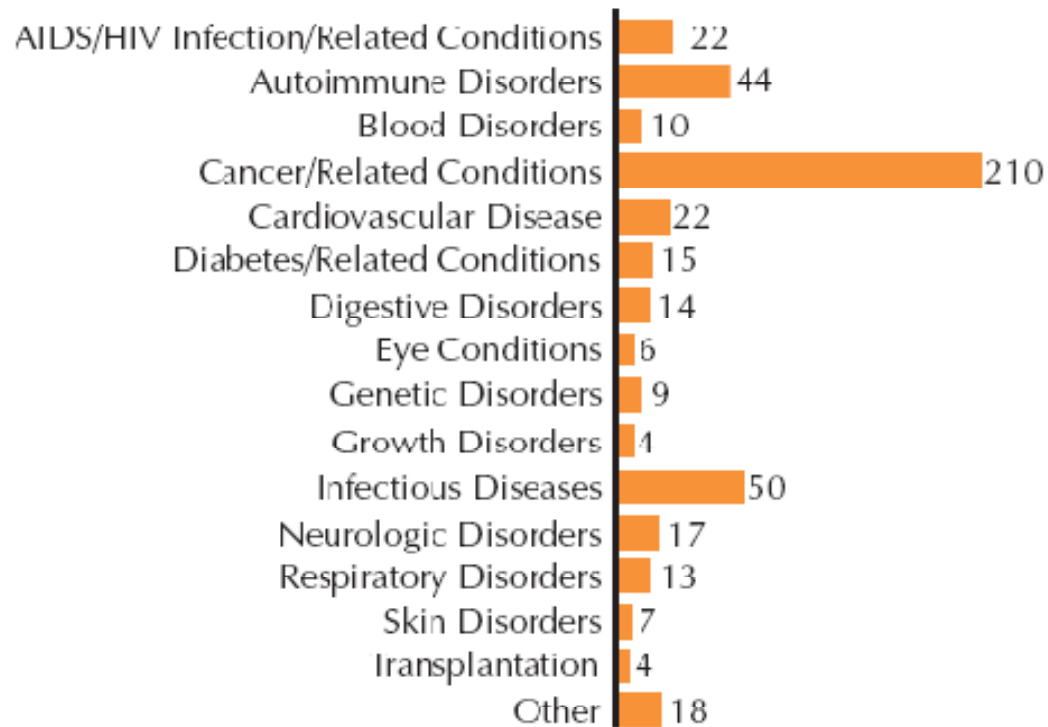
New medicines in development



Source: European Commission

# Biotech Medicines in Development for Many Diseases with No Effective Treatment or Cure

## BIOTECHNOLOGY MEDICINES IN DEVELOPMENT— BY THERAPEUTIC CATEGORY\*

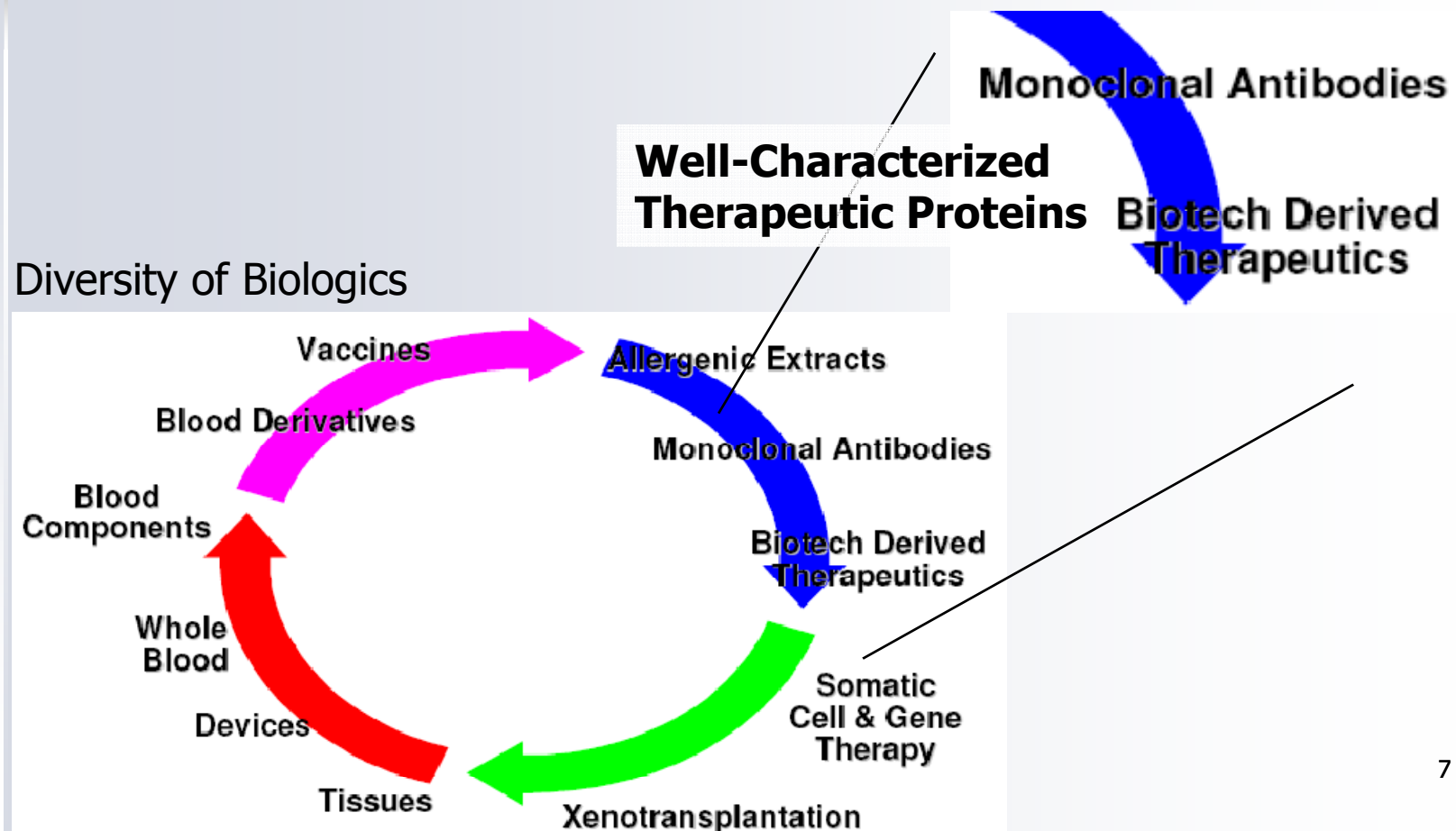


\*Some medicines are listed in more than one category.

# Biologics are...

- Derived from living material (plant, animal or microorganism)
- Derived from natural sources or engineered
- Usually based on a protein or nucleic acid
- Used for the treatment of diseases in humans

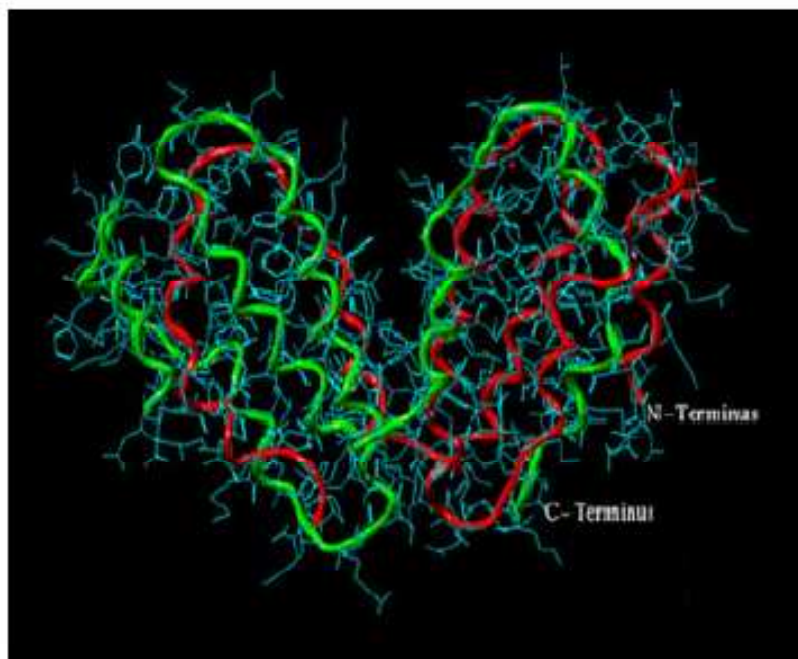
# A sub-set of biologics are relevant for Follow-on biologics applications: *Well-Characterized Therapeutic Proteins*



# Biologics are Different from Small Molecule (Chemical) Drugs

- **Composition, Size, Structure**
  - Larger, more complex, more heterogeneous
- **Manufacturing**
  - Genetic engineering vs. organic chemistry
  - Synthesis by living cells/organisms
- **Clinical Safety**
  - Species specificity limits standard pre-clinical models for safety testing
  - Usually injected
  - Immunogenicity

# Biologics are more complex than chemical medicines



**Interferon Beta**  
MW 19'000D



**Aspirin:**  
MW 180D

# Characteristics of Biologics Manufacturing Process

- Products are made from live cells
- Takes months, not weeks, to produce a run or batch
- To obtain consistent results, precise controlling necessary

# Immunogenicity—clinical concern for biologics, not for small molecule drugs

- Small molecule drugs rarely elicit immune responses
- Proteins (biologic drugs) are capable of triggering immune responses with varying consequences, e.g.,
  - Reduced effectiveness
  - Rare but life-threatening reactions
- Immunogenicity of biologic drugs is unpredictable, unforeseeable
- Small changes in a biologic molecule can completely shift its immunogenicity profile

## **This all translates into several key facts....**

- Biologic drugs are orders of magnitude more complex than small molecule drugs
- Safety & efficacy of final product exceptionally sensitive to small changes in manufacturing process
- It is difficult to impossible to predict the effect of these small changes—experience counts
- Potential for negative health consequences <sup>12</sup>

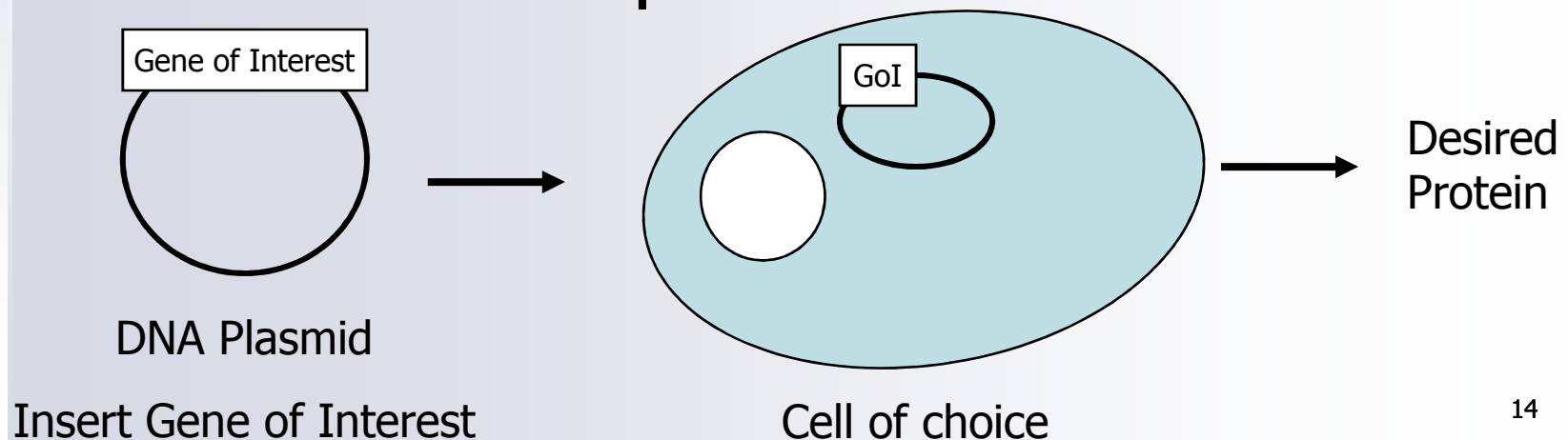
# Follow-on Biologics

## Scientific basis for approval

- Similar  $\neq$  Same
  - Everything else follows from this:
    - Require Clinical trials
    - Different names
    - No scientific basis for substitution/interchangeability

# Central Dogma of Molecular Biology--Biotech Revolution

- DNA makes RNA makes Protein
  - Inside a cell
- Manipulate DNA; Manipulate cells; Make desired protein



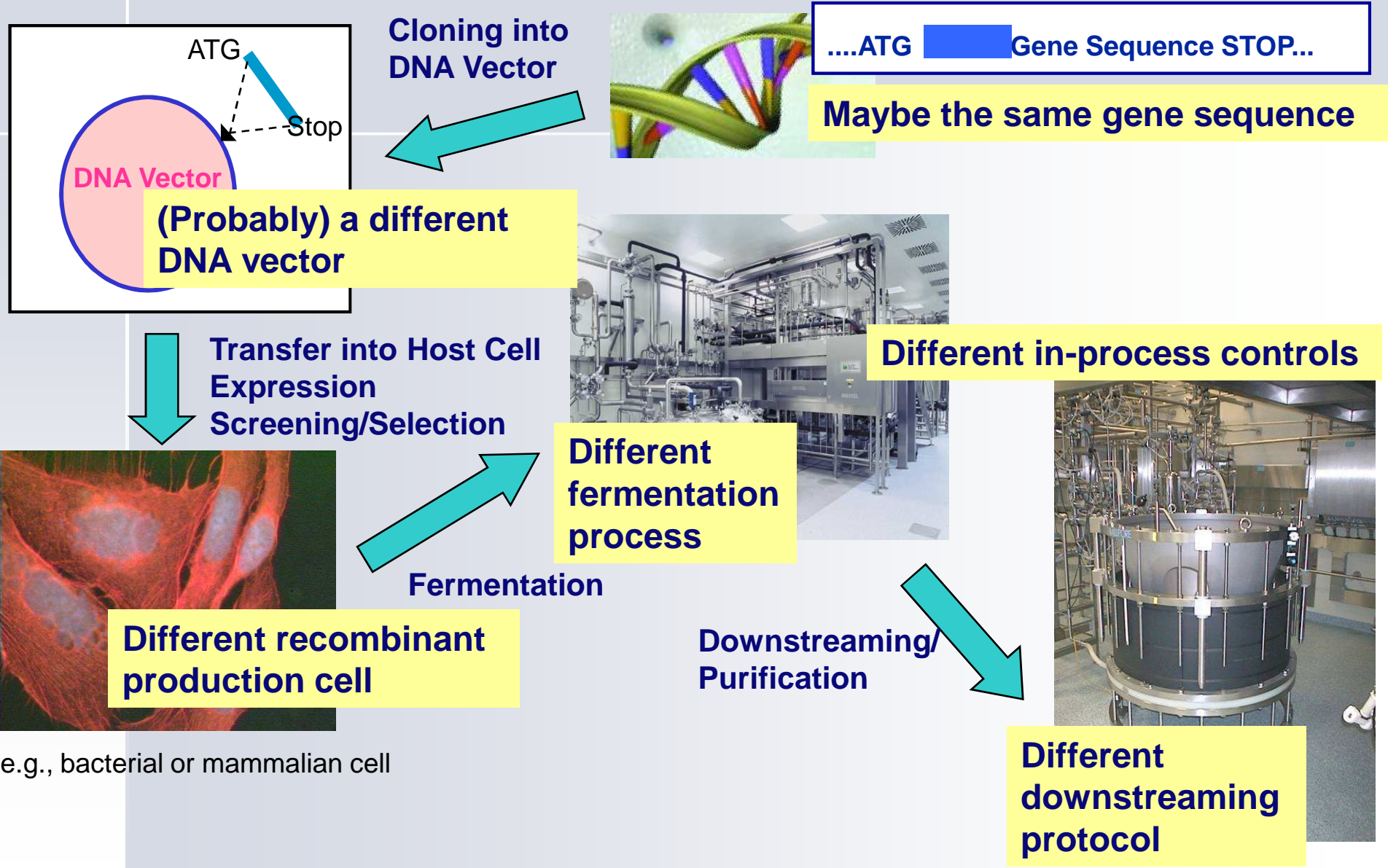
# Different cells will make slightly different protein

Cells w/GOI

Protein of Interest



# Different Protein Manufacturers Use...



# Same, different, similar

- Generic drug approval pathway premised on ability to make and show that generic drug is the same as the innovator drug
- Biologics from different manufacturers will be similar, not the same
- Therefore you need a different regulatory pathway, with different scientific standards
- Follow-on biologics are not generics
  - The regulatory pathway should reflect this in the rigor of the approval standards.

# Current science: Importance of Clinical Trials for Approval of Follow-on Biologics

- Similar proteins will have similar properties
  - For example, EPO will increase RBCs
- May not be possible to determine degree of molecular structural similarity
- Not possible to predict difference in clinical properties based upon understanding of structural similarity
- Need clinical safety and effectiveness data with each specific EPO to demonstrate it increases RBCs and its safety profile

# Immunogenicity—implications for FOB regulatory pathway

- Cannot be predicted in animal testing
- Pre-approval clinical testing necessary to rule out major quality or safety problems
- Adverse events generally extremely rare—need large populations to see
  - Won't see in typical pre-approval trials
  - Monitor in post-marketing setting
- Evidence that switching between products increases probability of immune response
- Tracking complicated if different products have the same name

## Follow-on Biologics should not be Subject to Automatic Substitution

- Generic drugs may be substituted for reference drugs because they are the **SAME**
- Follow-on biologics are similar to the reference, i.e., **DIFFERENT**
- No scientific basis to substitute different products

# Some arguments for substitution of similar products may jeopardize patient safety

- Close enough
  - “Proteins are similar and so should have the same clinical effect”
- “Same” clinical effect
  - E.g., aspirin and acetaminophen
  - Statins, as a class
- Doctors use them “interchangeably”

# Different things should have different names

- Generic drugs have the same name as their reference drug because they have the **SAME active ingredient**
- Follow on biologics will be similar to (i.e., **DIFFERENT** from) their reference product

# **No Harmonized Worldwide Regulatory Framework for Follow-on Biologics**

- Small molecule generics model is inappropriate
- In many regions limited or no regulatory processes exist
- Lack of minimum regulatory standards presents a risk for patients because of the potential issues relating to the quality, efficacy and safety of follow-on biologics developed and approved without defined requirements

# Follow-on Biologics--Summary

- The issues and the science are complex and multi-faceted.
- Patient safety and sound science are fundamental; biologics raise unique concerns because of the close relationship between a product's manufacturing process and its clinical attributes.
- Strong intellectual property protections are essential to promoting innovation that meets patients' needs through new biologics medicines.
- Extensive fact-finding through rigorous and transparent processes is needed.